Neural correlates of perceptual filling-in of an artificial scotoma in humans

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When a uniformly illuminated surface is placed eccentrically on a dynamic textured background, after a few seconds, it is perceived to disappear and be replaced by the background texture. Such texture filling-in is thought to occur in retinotopic visual cortex, but it has proven difficult to distinguish the contributions of invisible target and visible background to signals measured in these areas. Here, we used magnetoencephalography to measure time-dependent brain responses in human observers experiencing texture completion. We measured responses specifically associated with the filled-in target, by isolating neural population signals entrained at the frequency of flicker of the target. When perceptual completion occurred, and the target became invisible, there was significant reduction in the magnetoencephalography power at the target frequency over contralateral posterior sensors. However, even a subjectively invisible target nevertheless evoked frequency-specific signals compared with a no-target baseline. These data represent evidence for a persistent target-specific representation even for stimuli rendered invisible because of perceptual filling-in.

magnetoencephalography | perception | perceptual completion | visual cortex

Perceptual completion is the interpolation of information across visual space in regions where that information is absent, and this phenomenon is ubiquitous in human vision. For example, perceptual completion occurs across the blind spot in monocular vision, for real (1) and artificial scotomas (2, 3), when objects are viewed behind occluders (4) and for illusory contours (5). Whether common neural mechanisms underlie such disparate phenomena remains unclear. Here, we sought to identify the neural mechanisms associated with one type of perceptual completion caused by an artificial scotoma. A uniformly illuminated achromatic surface placed in the visual periphery on a background of dynamic luminance noise will fade after a few seconds to be replaced by the background (2), thus leading to an "artificial scotoma" in the visual field. Such texture filling-in has proven a useful model system with which to probe the neural mechanisms underlying perceptual completion. Unlike other forms of perceptual completion (e.g., across the blind spot), texture filling-in has a clearly defined latency and onset (3, 6), making it possible to study how it unfolds in time. Filling-in can also provide insight into the neural mechanisms of visual awareness in general, because changes in awareness occur without any change in physical (retinal) stimulation.

The time taken for an achromatic surface to fill in with surrounding texture is linearly related to the length of its bounding contour projected onto visual cortex (6). This strongly implicates retinotopic cortex as the neural substrate for such perceptual completion. However, neurophysiological investigations of texture filling-in have produced conflicting results. In awake nonresponding monkeys, texture completion is associated with increased activity in V2 or V3 (7); but in responding monkeys there are apparently no changes in activity in V1 and V2 (8). In humans, V1/V2 activity is reduced during luminance filling-in and activity increases in higher visual areas but with little evidence for any retinotopic specificity of these effects (9).

All these previous studies have focused on measuring cortical activity associated with perceptual completion that was retinotopically specific to the area of the scotoma. This has the potential disadvantage that it necessarily conflates the neural correlates of two distinct perceptual phenomena. First, the "positive effects" associated with filling-in of the textured background into the region of the visual field occupied by an achromatic surface. Second, the "negative effects" associated with the physically present achromatic surface that is no longer perceived. To differentiate these two factors, some way of distinguishing signals evoked by the perceptually filled-in target from the perceptually completed background is required. Retinotopic location alone cannot distinguish these signals because the positive and negative effects of texture completion occur at the same location in the visual field.

Here, we overcome this problem by using frequency-tagged magnetoencephalography (MEG) (10–12). We flickered a uniform target at 7.5 Hz and measured steady-state responses specific to this stimulus frequency in contralateral posterior MEG channels. These responses allowed us to assess how stimulus-related signals changed when perceptual completion unfolded in time. Because the signals were specific to the stimulus (and its corresponding retinotopic location), and not the background (which had a broad frequency spectrum), we could evaluate whether steady-state neuromagnetic responses persisted after perceptual completion. The presence of such signals would indicate an unconscious representation of the perceptually completed stimulus (7, 13, 14).

Results

A uniform surface flickered at 7.5 Hz in the near periphery on a background of random noise. After a few seconds of central fixation, subjects perceived an apparent disappearance of the flickering target and indicated this disappearance with a button press. In a proportion of trials (27%), the flickering scotoma physically disappeared. We measured steady-state MEG responses to periods when the flickering target was present and perceived ("flicker visible"), present but not perceived ("flicker filled-in"), and absent and not perceived ("flicker absent") (see *Methods* for full details).

Behavioral. All subjects reported reliable filling-in throughout the experiment and that they were unable to distinguish between periods of perceptual completion where the stimulus was physically present but perceptually filled-in and periods where the

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Fig. 1. Event-related fields. (*A*) Schematic topographic representation of the 275 channels in the MEG array. The locations of the representative sensors MRO22 and MLC11 have been highlighted. L, left; R, right. (*B*) Grand mean ERFs time-locked to the change in stimulus for 14 subjects recorded at MRO22, which was representative of right posterior channels during epochs when the peripheral flickering target was visible (blue), filled-in (green), and absent (red). Note that a sinusoidal ERF is seen, which is less prominent when the flickering target was filled-in and absent. (*C*) Grand mean ERFs for 14 subjects in a representative frontal channel, sensor MLC11, with minimal separation between the ERFs in the three conditions.

Fig. 2. Steady-state evoked responses. (*A*) Schematic topographic representation of the 275 channels in the MEG array. The locations of the right posterior channels used in further analyses have been highlighted. (*B*) Mean power-frequency spectra for steady-state evoked responses recorded from all channels in the right posterior quadrant and averaged across 14 subjects, during epochs where a peripheral flickering target was visible (blue), filled-in (green), and absent (red). Note the peaks at 7.5 and 15 Hz during epochs when the target was visible. (Flickering frequency white to black was 7.5 Hz and frequency of any change was 15 Hz.) A small peak in the α-range (9–11 Hz) is most prominent in the flicker-absent condition. Dashed lines indicate 7.5 and 15 Hz. (*C* and *D*) Normalized power in right posterior sensors at 7.5 Hz (*C*) and 15 Hz (*D*) compared among flicker visible, filled-in, and flicker-absent conditions. Data shown are averaged across 14 subjects with error bars representing standard error of the mean and the asterisk indicating statistical significance in a one-tailed paired t test ($P < 0.05$). Normalized power is in arbitrary units.

stimulus was physically absent. No visual aftereffects from the flickering stimulus were reported.

Perceptual completion was reliably experienced in the majority of trials, with at least 1 s of filling-in on 92.6% (SEM = 2.29) of trials. Within each trial, perceptual completion occurred with variable latency, but the change from beginning to fade to filled-in completely was rapid, with mean time from onset of fading to completely filled-in of 0.75 s (SEM = 0.16). Perceptual completion occurred at a mean latency across subjects of 4.0 s (SEM = 0.23) after trial onset; mean duration of filling-in was 5.0 s (SEM = 0.39), persisting to the end of the trial on most occasions.

Eye Position Data. Repeated-measures ANOVA showed no significant differences in grand mean eye movement from fixation between conditions for the 11 (of 14) subjects for whom eye-tracking data were available [$F (2, 20) = 2.56, P = 0.102$]. Thus, fixation was well maintained throughout, consistent with the high proportion of trials on which reliable filling-in was reported.

Event-Related Fields (ERFs). Fig. 1*B* shows the grand mean ERF across all subjects from a representative posterior sensor (see *Methods* for details), time-locked to the change in the flickering target from black to white, for each of the three conditions separately. During time periods where the flickering target was present and consciously perceived, a clear sinusoidal ERF was identified. When the flickering target was not perceived and when the target was absent, no clear ERF was seen. This effect was qualitatively present in 12 of 14 subjects in the right posterior sensors but was not seen in any subjects in frontal sensors (where no stimulus-evoked activity would be expected) (Fig. 1*B*).

Statistical parametric maps [see supporting information (SI) Fig. 5] of the reconstructed putative 3D sources (see *Methods*) of these ERFs revealed that the most reliable generator (at a threshold of $P < 0.001$, corrected) in occipital cortex for flicker visible and filled-in conditions was located in the upper bank of the right calcarine sulcus, consistent with the location of the flickering stimulus in the lower left visual field. In the filled-in conditions, additional generators were also identified in more lateral areas of

occipital cortex. Taken together, these findings suggest that signals associated with texture completion in humans may originate from structures including primary visual cortex. However, caution is required in interpreting these findings because of the very close proximity of the likely retinotopic sources for our stimulus, plus the known extensive intersubject variability in the spatial extent of retinotopic areas (15) even after spatial normalization. Nevertheless, these preliminary findings suggest that future investigation of texture completion using a technique with higher spatial resolution such as functional MRI may be promising.

Steady-State Analysis. Grand mean power spectra of steady-state evoked responses recorded from sensors over right posterior cortex (i.e., contralateral to the field of stimulation; see *Methods*) for the three conditions are shown in Fig. 2*B*. An overall 1/f pattern was apparent across all three conditions, as reported previously for steady-state responses to visual flicker (16). However, during epochs where the flickering target was clearly visible to the subjects, two additional peaks were seen, at 7.5 Hz (the frequency of change in the target from white to black) and at 15 Hz (the frequency of any change, i.e., from white to black and from black to white).

When the flickering target was physically present but perceptually filled-in by the background, smaller peaks in the power spectrum at 7.5 and 15 Hz were seen compared with when the stimulus was clearly visible. However, when the flickering stimulus was physically removed (but the filled-in background dynamic noise remained visible), these peaks were no longer present. Clearly visible stimuli evoked significantly greater power at stimulation frequencies compared with perceptually filled-in but physically present stimuli [$t (13) = 2.0, P = 0.027$ for 7.5 Hz, one-tailed t test;

Fig. 3. Topographic display of smoothed interpolated normalized power at 15 Hz at the middle time point within the epoch averaged across 14 subjects (see *Methods*). Color indicates normalized power in arbitrary units. During epochs where the stimulus was physically present (flicker visible), greatest power is seen in the right posterior quadrant, contralateral to the visual field of stimulation. During epochs when the stimulus was filled-in, greatest power is still seen in the right posterior quadrant, but the power is reduced compared with epochs where the flickering stimulus was perceived. Where the stimulus was physically removed, (flicker absent) low power is seen bilaterally in the posterior cortex. Note that with the axial gradiometer MEG system used, these data should not be interpreted as suggesting that the hotspot overlies the area of maximal activity.

t (13) = 2.1, P = 0.035 for 15 Hz, one-tailed t test]. Similarly, when stimuli were physically present but phenomenally filled-in, there was significantly greater activity than for the same perceptual appearance but when the stimulus was physically absent [t (13) = 1.8, P = 0.046 for 7.5 Hz; t (13) = 2.087, P = 0.029 for 15 Hz].

Topographic Displays. Fig. 3 shows interpolated topographic maps of normalized power at 15 Hz, the frequency of any change in the target, corresponding to epochs where the flickering target was visible, filled-in, and physically absent. During epochs where the stimulus was physically present, greatest power was seen in the right posterior quadrant, contralateral to the visual field of stimulation, confirming the retinotopic specificity of our effects. During epochs when the stimulus was filled in, the greatest power was still seen in the right posterior quadrant, but the power was reduced compared with epochs where the flickering stimulus was perceived. The topographic map for epochs where the stimulus was physically removed demonstrated low-power bilaterally in the posterior cortex. Qualitatively similar maps were apparent for smoothed normalized power at 7.5 Hz. Similar topography across all conditions suggests that similar neural generators are responsible for the differences in power in the frequency-tagged spectral components identified above.

Discussion

We studied the neural correlates of perceptual completion using frequency-tagged MEG to isolate neural representations of a flickering target placed on a dynamic noise background. Power in posterior sensors contralateral to the target was significantly reduced when the flickering target was filled in, consistent with stronger neural representation in visual cortex for visible compared with perceptually filled-in stimuli. However, the flickering target still evoked neural signals (compared with no-stimulus baseline) even when subjectively invisible and filled in. Note that signals from epochs where the target was gradually fading from awareness were removed from our analyses, so our findings reflect activation associated with epochs when the target was entirely invisible. There was therefore a persistent neural representation of the invisible target. Consistent with previous reports, modulation of stimulus-associated signals by conscious perception was somewhat stronger than by physical stimulus characteristics (17, 18).

The neural mechanisms of such texture completion in humans have only rarely been studied. Consistent with our findings, functional MRI (fMRI) signals from contralateral V1/V2 are reduced for perceptual completion of small gray targets placed eccentrically

on a uniform achromatic background (9). However, such reductions in signal are not confined to the retinotopic location of the target but extend into representations of the background. Because of the point-spread of the hemodynamic response (19), it remains unclear to what degree these effects are contaminated by signals from the immediate surround or reflect signals originating from the retinotopic location of the filled-in surface. In contrast, here, we overcame this problem by using frequency-tagged MEG. The spatial resolution of MEG is poor compared with fMRI. But because the target flickered at a specific frequency, we could isolate neural populations responding specifically to the target and not the background even after filling in had occurred. It is possible that frequency-specific responses might spread over the cortical surface beyond the precise retinotopic location of the target; but critically, such responses were specifically associated with the target and not the background.

We studied how the population responses of neurons in visual cortex entrained by the flickering target changed as a function of subjects' perceptual reports. In contrast, previous studies in monkey examined perceptual completion in animals that did not report their perceptual state (7, 20, 21). During texture filling-in, neurons in V2/V3 show increased firing over a time course comparable with filling-in reported behaviorally in humans (7). However, during chromatic filling-in, neurons in V1 with receptive fields at the target borders exhibit reduced firing, whereas those with receptive fields at the target center show no change in firing rates (8). Differences between studies may arise from the different visual paradigms used to elicit perceptual completion. Nevertheless, without clear and consistent behavioral reports of whether perceptual filling-in occurred in all these previous studies, it is difficult to draw firm conclusions. In contrast, the present study combined behavioral reports with measures of population activity to show that filling-in is specifically associated with a reduction in activity of neural representations of the filled-in target.

The extent to which other types of filling-in (e.g., across the blind spot) share common neural mechanisms with the texture completion studied here remains to be established. One potentially important phenomenal distinction is that texture completion is not instantaneous but has a defined latency and onset. In humans, completion across the blind spot or in other areas of retinotopic V1 (22, 23) is associated with enhanced activity in the retinotopic location where completion takes place. Unlike the present study, this previous study did not explicitly "tag" signals associated with the target that was filled in. Thus, signals associated with perceptual completion in V1 may represent the neural correlates of the perception of the filled-in background rather than the overwritten target.

Our finding of reduced MEG power when a previously visible stimulus became invisible because of texture completion suggests a reduction in the strength of neural representation in visual cortex for invisible (versus visible) stimuli. Consistent with this, frequency-tagged EEG and MEG studies also demonstrate reduced power for stimuli that become invisible during binocular rivalry (10, 24). Moreover, recent fMRI studies consistently find that signals from human ventral visual cortex are reduced when stimuli are invisible, compared with identical physical stimulation that results in conscious perception (25, 26). Thus, a consistent general feature of the human visual system is of stronger neural activity associated with conscious perception of a stimulus compared with equivalent physical stimulation that remains unconscious (27). Moreover, MEG and fMRI studies are consistent, despite the very different aspects of population neural responses recorded by the different techniques. Some studies have also shown that additional areas of parietofrontal cortex are activated when a visual stimulus is consciously perceived (28–30). In the present study, increased power associated with target visibility was restricted to contralateral occipital sensors. However, our frequency-tagging approach deliberately isolated signals where neuronal population responses are

entrained by the frequency of visual stimulation. Thus, it would not be expected to reveal activity associated with perceptual completion in neuronal populations that are not strongly driven by retinal input (16), such as those outside occipital cortex.

Importantly, we found that target-specific responses were reduced but not eliminated during filling-in. This indicates the presence of a persistent neural representation of subjectively invisible stimuli. Consistent with this finding, several fMRI and EEG studies have shown that ventral visual cortex can retain a neural representation of subjectively (and objectively) invisible stimuli (25, 26, 31–33). Our findings go beyond this earlier work by extending such observations to the new situation of low-level perceptual completion, further confirming that activation in visual cortex is not sufficient for conscious awareness.

Filling-in of the flickering stimulus necessarily followed a period when the stimulus was visible. However, our findings of maintained but reduced power after filling-in cannot be due to entrainment of MEG responses when the stimulus was visible persisting into the period of perceptual completion. To rule this out, we removed the first 400 ms of data recorded after filling-in or after the physical withdrawal of the target. Findings were unchanged compared with when these data were included in the analysis, suggesting that continued power measured at 7.5 Hz during filling-in was not due to entrainment. Furthermore, our findings of reduced power when the stimulus became invisible during filling-in was in the opposite direction to the recognized increase in power that occurs with visual steady-state responses during the first few seconds of stimulus presentation (34). (Although an adaptation decline does occur, this begins only after 10 s of stimulation, which is longer than the duration of the entire trial in the current experiment.) Such a tendency to increase would, in any case, be in the opposite direction to the observed reduction in power when the stimulus became invisible due to filling-in.

We monitored eye movements throughout. Accurate fixation is necessary for filling-in and subjects were asked to continually monitor the target location even after disappearance to ensure continued invisibility. Consistent with this, we did not find any significant differences in eye position or movements comparing the three different perceptual states (target visible, invisible, or absent). The angular resolution of our infrared eye tracker was insufficient to rule out the possibility that there were different frequencies of microsaccades in the different perceptual states (35). However, any such microsaccades will not occur at a precise regular frequency of 7.5 Hz or 15 Hz and so can neither account for our finding of decreased power at the specific frequency tagged by the flickering target during filling-in nor for a persistent frequency-tagged representation of the invisible stimulus.

Our frequency-tagging approach isolated signals specifically associated with the target. After filling-in had occurred, subjects nevertheless perceived the textured background at the location in the visual field previously occupied by the (now invisible) target. The continuing presence of a target-specific MEG response to this invisible target therefore indicates that a retinotopically specific representation of the target coexists with a phenomenal percept of a different texture at the same location in the visual field. This may provide some constraints for theoretical or computational accounts of perceptual completion. Specifically, it is not consistent with accounts that posit that the phenomenal experience of perceptual completion is just the brain "ignoring an absence" (36). Instead, our findings are more consistent with filling-in being associated with neural signals that represent a presence rather than ignoring an absence (6, 37). However, the persistence of the invisible target signal during perceptual completion suggests that there must be additional brain mechanisms that suppress the target in awareness in favor of the background. These could include feedback connections from higher brain areas, reflecting top-down control of this process taking place in early visual cortex. Future research will be needed to specifically examine this possibility.

Conclusion

Target-specific responses of human contralateral visual cortex are reduced when a target is rendered invisible by perceptual completion. However, even when invisible, target-specific responses remain, indicating that both the invisible target and the perceptually completed background may be represented at the same retinotopic location.

Methods

Subjects. Seventeen neurologically normal adults (five females, 18–36 years old) with normal or corrected-to-normal vision gave written informed consent to participate in the study, which was approved by the local ethics committee. One subject was rejected because of excessive head movement (mean >1.5 mm), one was rejected because of falling asleep during the experiment, and one was rejected because of misunderstanding experimental instructions. Fourteen subjects (four females, 18–36 years old) were therefore included in the analyses reported here.

Stimuli. Stimuli consisted of full-field random dynamic achromatic noise (subtending $33 \times 24.8°$) with a red central fixation cross (0.2°) and a flickering peripheral target. Stimuli were projected by using an LCD projector (Sanyo, Osaka, Japan) PRO xtraX, refresh rate 60 Hz, screen resolution 640×480) through a porthole and two mirrors onto a projection screen mounted in front of the subject. All stimuli were presented with MATLAB (Mathworks, Sherborn, MA using the COGENT 2000 toolbox (www.vislab.ucl.ac.uk/cogent/index.html). To generate random dynamic noise, we created 30 arrays of 200×200 pixels, each measuring 0.165 by 0.124° that were pseudorandomly assigned a gray-scale at the start of each run. These 30 arrays were then presented in a pseudorandom order at the screen refresh rate (60 Hz) to give the appearance of random dynamic noise with a mean luminance of 20.7 cd/m^2. An artificial scotoma was created by placing a small flickering square achromatic target (1.12 by 1.12°) on the background in the lower left visual field at 9.43° eccentricity (8° across, 5° down) flickering between black (luminance 2.5 cd/m^2) and white (luminance 98.4 cd/m^2) at a rate of 7.5 Hz (eight screen-refresh cycles). This frequency was chosen because it produces the largest amplitude oscillatory MEG signal (38). The lower half of the visual field was chosen for placement of the target, because filling-in has been shown to be more robust (9) and because MEG signals have been shown to be stronger for stimuli presented in the lower visual field (39). In behavioral experiments before scanning, we confirmed that the target was small enough to allow filling-in to occur, despite the pertinent flickering, but large enough to detect by using steady-state MEG responses.

Procedure. On each trial, subjects were presented with a screen of dynamic noise and a flickering target in the near periphery. Subjects were instructed to fixate centrally and indicate disappearance of the peripheral target by using a button press (see Fig. 4). On some occasions, the stimulus was perceived to fade for a short time before disappearing and subjects could indicate this fading with a different button press. Subjects indicated any reappearance of the target (for example after loss of central fixation) with a third button press. These button presses were used to define time-periods of flicker-visible, flicker-faded, flicker-filled-in, and flicker-returned. Each trial lasted 10 s and was followed by a 500-ms interval during which a gray screen (luminance 15.0 cd/m^2) was presented. A small red fixation mark was always present centrally. Optimal trial length was determined before scanning. In a proportion of trials (27%) the peripheral flickering stimulus physically disappeared 5 s after trial onset, whether the subject was reporting filling-in or not. Because the target had been flickering, there were no stimulus-contingent aftereffects. The periods of time after the stimulus had physically disappeared were defined as flicker-absent time periods. Each
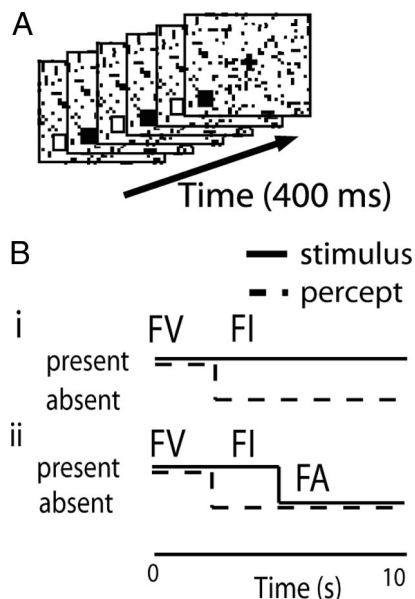
Fig. 4. Stimulus presentation. (*A*) Stimulus configuration. Visual stimuli consisted of full-field random dynamic achromatic noise with a small square achromatic target in the lower left visual field flickering at a rate of 7.5 Hz. (*B*) Procedure. (*i*) Normal trials: During each 10-s trial, subjects fixated centrally and indicated the perceived disappearance of the flickering target. Time periods were defined as "flicker-visible" (FV) while the target was present and perceived and "filled-in" (FI), while the target was present but not perceived. This filling-in occurred at a variable time after stimulus presentation, depending on subjects' perception. (*ii*) Catch trials: During 27% of trials, the flickering target was physically removed 5 s after the onset of the trial. During these trials, periods were defined as "flicker visible" for target present and perceived, "filled-in" for target present but not perceived, and "flicker absent" (FA), for target absent and not perceived.

subject completed five runs, each comprising 55 trials, and received quantitative feedback at the end of every run as a percentage of trials where they had reported filling-in for >1 s. Subjects were encouraged to blink during specific rest periods during recording but were not told to abstain from blinking during the rest of the experiment. All subjects received training before scanning to ensure that they could experience disappearance of the stimulus and assign consistent responses to different perceptual states.

MEG Acquisition. MEG data were recorded by using 275 third-order axial gradiometers using the Omega275 CTF MEG system (VSMmedTech, Vancouver, BC, Canada) at a sampling rate of 240 Hz within an electromagnetically shielded dimly lit room. Subjects were seated and viewed computer-generated stimuli projected through a porthole and two mirrors onto a screen at a distance of 57 cm. Trigger events were recorded at every change of the target from black to white, where the stimulus was visible, and at the equivalent time when the flickering target was absent. Each subject's head position was determined by using three coils attached to anatomical landmarks (nasion, right, and left preauricular points) at the beginning and end of every run. In a separate session, a photodiode was placed on the screen at the position of the flickering target to record the precise timing of the flicker and determine screen latency.

MRI Acquisition. T1-weighted volumetric anatomical images were acquired with either a 3T Siemens (Erlangen, Germany) Allegra system ($n = 11$) or a 1.5T Siemens Sonata system ($n = 3$), according to scanner availability. (Dimensions $224 \times 256 \times 176$, slice thickness = 1 mm). Fiducial points were marked by using vitamin E capsules.

MEG Analysis. MEG data were analyzed by using SPM5 (Wellcome Department of Imaging Neuroscience, London, U.K.; www.fil.ion.ucl.ac.uk/spm). For all analyses, each 10-s trial was divided into separate time periods according to the subjects' button-press responses and taking into account any times where the target had been physically removed from the screen (see above). Thus, three different time periods, or conditions, were defined across all trials as follows:

1. Flicker visible. In this time period, the flickering target was present on-screen, and subjects indicated that they clearly perceived it by the lack of button-press.
2. Flicker filled-in. In this time period, the flickering target was present on-screen, but subjects indicated that it was invisible, with the dynamic noise appearing in its location through perceptual completion. This condition is physically identical to flicker-visible but differs in conscious perceptual state.
3. Flicker-absent. In this time period, the flickering target was absent and replaced by dynamic noise. Note that this condition is perceptually identical to flicker-filled-in but differs in physical stimulation because of the absence (versus presence) of the flickering scotoma. (Fig. 4*B*)

Time periods between flicker-faded and flicker-filled-in button presses were discarded because these were most variable between and within individuals in terms of subjective experience. Furthermore, as the subjects improved at the task, the transition between faded and filled-in became increasingly short, so that for most subjects, the flickering stimulus disappeared without fading.

ERFs. For the computation of event-related averages, the data were band-pass filtered at 1–45 Hz (Butterworth), and from each time period defined by subject responses, 180 ms epochs were extracted from the time series 50 ms before the trigger event, when the target changed from black to white, and 130 ms after the trigger event. Short epochs were used to capture the first trigger-related responses, to avoid loss of signal because of jitter. Extracted data were baseline-corrected and down-sampled, and individual 180-ms epochs containing blinks or saccades >2° were discarded. An artifact criterion of ± 950 fTesla ($n = 12$) or ± 1,150 fTesla ($n = 2$) was used to reject trials with excessive EMG or other noise transients. Data were then averaged across trials for the same condition, and a grand mean for all subjects was calculated for each condition.

3D Source Reconstruction of ERFs. Source reconstruction was performed in SPM5 (Wellcome Department of Imaging Neuroscience; www.fil.ion.ucl.ac.uk/spm) by using a distributed source solution based on a mesh of 3,004 vertices derived from individual subjects' structural MRI. Event-related fields were then coregistered into structural MRI space by using a landmark-based coregistration based on fiducial position (nasion and left and right preauricular). Fiducials in MEG space were matched to the corresponding MRI space by using rigid transformation matrices. The same transformation was then applied to the sensor positions. Forward computation was performed by using a single-sphere method. Inverse reconstruction of the evoked response used an empirical Bayesian approach (40). The entire time series for each condition was reconstructed. The peak absolute value for each condition in each subject was found and the source estimation for that time point used in further analyses. Values were normalized to the mean and then converted into voxel space and smoothed with a 12-mm FWHM Gaussian kernel. Multiple linear regression was then used to generate parameter estimates for each condition at every voxel for every subject. The resulting parameter estimates for each condition at each voxel were then entered into a second-level analysis, where each subject served as a random effect in a one-tailed t test. Appropriate corrections were made for nonsphericity and correlated repeated measures (41). For these whole-brain analyses, a statistical threshold of $P < 0.001$ corrected for multiple comparisons was used.

Steady-State Analysis. Data were band-pass filtered at 1–45 Hz (Butterworth) and from each of the time periods defined by subject responses, consecutive, nonoverlapping 500-ms epochs were extracted from the time series. Each epoch was extracted exactly at one of the trigger events, where the target changed from black to white, to ensure phase-locked averaging (16), with epochs starting 100 ms before the trigger and lasting until 400 ms after the trigger. Because epochs were nonoverlapping, not every trigger was used as a start point to extract data. The first 500 ms epoch from every 10-s trial was discarded to remove onset effects and allow build up of steady-state. The extracted data were baseline-corrected and downsampled to 100 Hz. Epochs containing blinks or saccades >2° were discarded. Artifacts were also discarded by using thresholds specific for individual subjects, as above. These epochs were then averaged across trials for the same condition. Mean number of epochs per condition was 1,207 (SEM = 91.5) for flicker-visible, 1,708 (SEM = 174) for filled-in, and 529.9 (SEM = 34.1) for the flicker-absent condition. Quantification of the evoked oscillatory activity was performed by using a wavelet decomposition of the averaged MEG signal across a 2–45-Hz frequency range, by using a complex Morlet wavelet, with a width of 7 cycles [as used elsewhere (42–44)].

Before statistical testing, the frequency spectra were normalized to the mean of the power at 30–45 Hz at the middle 20 ms of each 500-ms epoch (140–160 ms) at each of 58 sensors in a quadrant over the right posterior cortex (Fig. 2A). As the steady-state phenomenon ran across the whole of each condition, we chose the middle of each epoch to avoid loss of specificity at the borders of the epochs. All analyses were carried out on power data and therefore included no negative values, such that averaging did not result in cancellation of field patterns. Differences between pairs of conditions, for the mean of sensors in the right posterior quadrant (Fig. 2), were tested for statistical significance by using a one-tailed paired Student's t test, with $P < 0.05$ indicating significance.

Topographies were produced by linearly interpolating sensor information at 14–16 Hz at the middle 20-ms time point onto sensor space. These were then smoothed by using a Gaussian kernel (FWHM 6 mm) and normalized to the mean of the power at 30–45 Hz. We examined the power at 15 Hz, double the stimulus frequency of 7.5 Hz, because the fundamental response to patterned stimuli occurs at double the stimulus frequency (45).

Eye Movement Recording and Analysis. During scanning, eye position and pupil diameter were continually sampled at 60 Hz by using infrared video-oculography (Iview X Hi Speed Tracking System; Tracksys SensoMotoric Instruments, Nottingham, U.K.). Eye movements were monitored online by means of a video screen for 11 subjects. For technical reasons, eye movement data could not be recorded in three of the included subjects.

Eye-tracking data were analyzed with MATLAB (Mathworks). Epochs with blinks and saccades >2° were removed from the MEG data. Mean rejection rate due to blinks and saccades was 21.2% for flicker-visible (SEM = 3.95), 19.7% for filled-in (SEM = 3.53), and 25.4% for flicker-absent conditions (SEM = 3.20). Mean eye position, expressed as distance from fixation, was then computed for the residual eye tracking data for each condition and every subject from whom data were available. A repeated-measures ANOVA was used to establish whether mean eye position deviated significantly from fixation or between conditions.

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